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VITAMIN REVIEW. II.

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VITAMIN REVIEW. II.

By **RUTH WOODS**

The present section of the Vitamin Review will include folic acid, vitamins A, D, E and K, ascorbic acid, vitamin P and a listing of the unidentified lesser vitamin factors, as well as a chart summarizing the known human requirements for the vitamins as recommended by the National Research Council.

Folic Acid:

Folic acid is the popular descriptive term for a group of closely related compounds recently identified as new factors of the vitamin B complex. Folic acid (specifically the *L.casei* factor from liver) was isolated during the past year and identified chemically as pteroylglutamic acid. Pteroylglutamic acid is composed of three main groupings: (1) A two-ringed nitrogen compound, a pteridine (a type of yellow pigment first isolated from butterflies' wings); (2) *p*-aminobenzoic acid; (3) glutamic acid. Pteroylglutamic acid has been synthesized and is represented by the formula depicted in Fig. 1. Pteroylglutamic acid is a bright yellow substance, slightly soluble in water as the acid and fairly soluble as the salt. It is readily destroyed by heat in acid media and its solutions undergo deterioration upon exposure to sunlight. There is an appreciable loss of folic acid in foods stored at room temperature and in cooking processes.

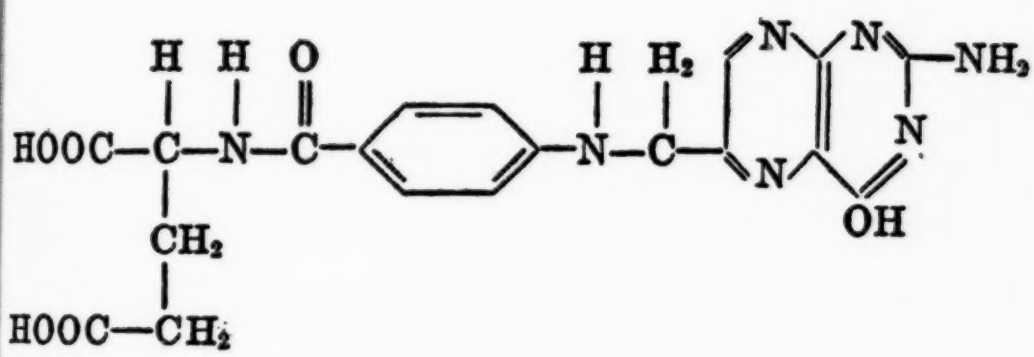

FIG. 1 FOLIC ACID
pteroylglutamic acid

Terminology: Before the identification of the liver *L.casei* factor as pteroylglutamic acid, it was observed that there was widely distributed in natural products a group of interrelated substances which were variously referred to as factor U, vitamin B_c, vitamin M, folic acid, *L.casei* factor and *S.lactis* R factor, depending upon the source of the material and the species of organism used for test purposes — chick, monkey, rat, lactobacillus casei. There was much evidence that the several factors all had a common chemical structure but differed from each other by (a) the presence of extra chemical groups attached to the parent molecule which made these

forms available only to certain organisms, or (b) the absence of certain parts of the common structure which restricted availability to those organisms which could synthesize the missing moiety. The folic acid group consists of four major compounds, namely:

1. Pteroylglutamic acid (natural *L. casei* factor from liver).
2. Pteroyltriglutamic acid (fermentation *L. casei* factor obtained from the anaerobic fermentation of a diphtheroid-type organism).
3. Pteroylheptaglutamic acid (vitamin B_c conjugate from yeast).
4. Pteroic acid (a synthetic form obtained by substituting *p*-aminobenzoic for *p*-aminobenzoylglutamic acid in the synthesis).

Activity: Pteroylglutamic acid is active for the chick, rat, monkey, turkey, guinea pig, *L.casei* and *S. lactis* R. Pteroyltriglutamic acid, which has two additional glutamic acid molecules, can generally be substituted for the simpler compound in most species. Pteroylheptaglutamic acid contains six extra glutamic acid molecules which have the effect of rendering the compound biologically unavailable except in the presence of an enzyme *(vitamin B_c conjugate)* which splits off the six glutamic acid molecules and liberates the rest of the compound. Chicks and rats can utilize this conjugated form of folic acid, but microorganisms can utilize it only to a very limited extent. The nutritional availability of the conjugated form for various species has not yet been completely evaluated, but it is thought that vitamin B_c conjugate is probably not readily available to the monkey or to man.

Functions: The biochemical role of folic acid has not yet been determined. Its nutritional effects on various species, however, have been clearly delineated. It is an essential growth factor for many microorganisms, particularly *L.casei.* It prevents a characteristic anemia in chicks, monkeys and man and cures sulfonamide-induced anemias in rats. It has been found to exert an inhibitory effect on certain types of spontaneous and experimentally induced carcinomas in mice. Lactation in rats and hatchability of chick eggs improve with administration of folic acid. Folic acid deficient chicks also exhibit disturbances in endocrine function. Turkeys develop a characteristic paralysis and guinea pigs develop a fatal deficiency disease accompanied by weight loss, lethargy and convulsions. Synthetic folic acid has been dramatically spotlighted recently because of its effectiveness in treating a number of clinical conditions—the macrocytic anemias of pregnancy, pellagra and sprue, nutritional macrocytic anemia and Addisonian pernicious anemia. The diarrhea and other symptoms of both tropical and non-tropical sprue also respond to folic acid therapy.

Requirements: Requirements for folic acid have not yet been set. Empirical dosages have been used and vary with the species and the condition to be treated. Tests show that pteroylglutamic acid is essentially nontoxic. The lethal dose is reported as 125 to 600 mg. per kilogram depending upon the species of test animal. This is five hundred to five thousand times the therapeutic doses which have been used successfully in sprue and pernicious anemia. Folic acid can be used to replace liver therapy in pernicious anemia without producing the unfavorable reactions sometimes encountered in persons sensitive to liver extract.

Sources: Liver, yeast, kidney, green leafy vegetables, cauliflower, beef, veal and dry breakfast cereals prepared from wheat.

Vitamin A:

Vitamin A is also known as the anti-xerophthalmic vitamin and, not quite accurately, as the anti-infective vitamin. The physiological effect of vitamin A is brought about in man and in animals by a number of different, naturally occurring and synthetic compounds known as carotenoids. The carotenoids or carotenes occur in plants. They are converted to "vitamin A" in the body in which form they are biologically available to the animal. Because they give rise to vitamin A, the carotenes are known as "pro-vitamins A." Vitamin A itself occurs only in animal products chiefly in fish liver oils. At least nine different naturally occurring pro-vitamins A and two vitamins A are known, although it is believed that many more probably exist. Vitamin A_1 is the most common form; vitamin A_2 occurs in fresh water fish. The most important pro-vitamins A are α-, β,- and γ- carotene and cryptoxanthine, of which β-carotene is the most efficient precursor of vitamin A. The structural formula for vitamin A is shown in Fig. 2. Vitamin A is fat soluble and stable to heat, acids and alkalis. It is destroyed by light and is sensitive to oxidation especially in the presence of rancid fat. It acts synergistically with vitamin E which protects vitamin A apparently by virtue of its anti-oxidant properties.

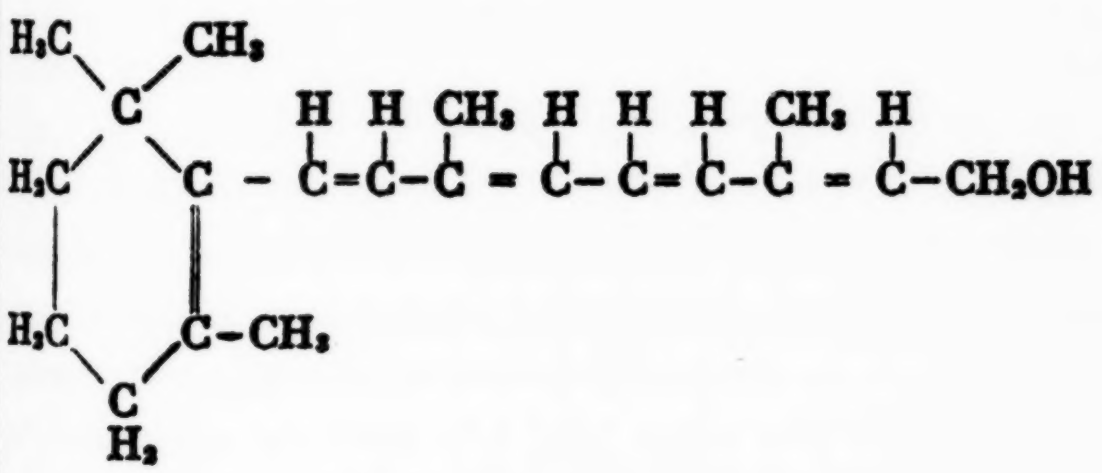

FIG. 2 VITAMIN A_1

Functions: The principal role of vitamin A is to stimulate the building of cells. It also exerts certain effects on fat and carbohydrate metabolism, but these have not been too clearly defined. Vitamin A in conjunction with a specific protein plays an essential role in the visual mechanism involving light and color vision and as such possesses a relationship similar to that of the B vitamins as a biological coenzyme. Vitamin A is used for the synthesis of rhodopsin, the "visual purple" which is a carotenoid-albumin.* Rhodopsin is continually bleached out under light and regenerates in the absence of light. Deficiency of vitamin A, therefore, interferes with the regeneration of rhodopsin and results in a decreased ability for dark adaption vision.

Because the major action of vitamin A is as a stimulus for new cell growth, a deficiency results in generally retarded growth. Specifically, there is atrophy of the protective lining in epithelial tissue, occurring first in the mucous lining of the respiratory tract. The degeneration of this protective tissue increases susceptibility to respiratory infection, which is why vitamin A has come to be regarded popularly as the "anti-infective" or "anti-cold" vitamin. Following degeneration of the respiratory mucosa, the mucous lining of the mouth and salivary glands is next affected and finally that of the eyes, intestinal tract, urethra and kidney. Dryness of the skin and hair often follows. Gastrointestinal disorders may occur and stones may be formed in the bladder and kidney.

Vitamin A deficiency causes various lesions of the eye beginning with the mild symptom of night-blindness (related to visual purple). This may progress through softening and perforation of the cornea to the condition known as nutritional xerophthalmia in which the eye becomes dry and lusterless and covered with white deposits. Vitamin A deficiency may influence the development of near-sightedness and may sometimes cause blindness by interfering with the optic nerve and canal. Vitamin A deficiency in pregnant animals has been found to result in blindness or even complete absence of eyeballs in the young.† Vitamin A is important also in normal tooth and bone development. Vitamin A deficiency can be detected in its earliest stages by determining the vitamin A and carotene levels in the blood. Reproduction in experimental animals is impaired by vitamin A deficiency. Providing amounts of vitamin A in excess of so-called minimum adequate levels has been found to increase the vigor and life span of animals and to prolong the "prime of life" period.

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*For a detailed explanation of the role of vitamin A in vision see *Borden's Review of Nutrition Research,* December, 1942, "Nutrition and Vision—Vitamin A."

†*cf. Borden's Review of Nutrition Research,* November, 1944, "Dietary Causes of Congenital Abnormalities."

Requirements: All mammals, birds and fish utilize vitamin A, but it is not certain that the vitamin is required by other species. There are indications that certain insects, for example, can dispense with it. Man and domestic and laboratory animals, however, all need vitamin A or its precursors. Double requirement standards are recognized, one for carotene and one for vitamin A. Carotene has half or less the value of vitamin A. The vitamin A requirements of adult animals are correlated with body weight, about 40 I.U. of β-carotene or 20 I.U. of vitamin A being minimum required values per kilogram of body weight. About five times this amount of carotene and three times the amount of vitamin A are considered optimal. This would bring the optimal average adult requirement to 5,000 I.U. of vitamin A per day. Increased amounts are required during adolescence, pregnancy and lactation.

Vitamin A in moderately large doses is non-toxic. Certain toxic reactions, however, have been observed in animals and in Arctic explorers as a result of eating telang or polar bear livers. The toxicity was traced to the extraordinarily high vitamin A content of these livers. A clinical case of apparent vitamin A toxicity in a baby fed 240,000 I.U. of vitamin A per day (as halibut liver oil) for almost three years has been reported; recovery from symptoms followed removal of supplementary vitamin A from the diet. Toxic symptoms resulting from overdosage with carotene include chiefly yellow discoloration of skin; from overdosage with Vitamin A, enlargement of liver and spleen, drying and peeling of skin, loss of hair, nausea, headache, weakness and blood dyscrasias.

Sources: Vitamin A is found in fish liver oils, liver, egg yolk, cream cheese, butter, fortified margarines, cream, ice cream and milk. (Vitamin A_1 occurs in salt water fish; vitamin A_2 in fresh water fish). Carotene occurs chiefly in green leafy plants such as kale, chard, escarole, beet greens, broccoli, spinach; also in apricots and yellow vegetables like squash, pumpkin, carrots and sweet potato. Cryptoxanthine is found in yellow corn and egg yolk. Carotenes and vitamin A esters isolated from natural sources are commercially available. A process for commercially synthesizing vitamin A was reported some months ago.

Vitamin D:

Vitamin D_1, the antirachitic vitamin, is also known popularly as the "sunshine vitamin." There are many forms of vitamin D and of its precursors, the pro-vitamins D, but only two forms of the vitamin are sufficiently potent to be of clinical interest. These are (1) irradiated ergosterol, also called calciferol, viosterol or vitamin D_2 and (2) natural vitamin D which is found in fish liver oils and which is formed in the skin of man and animals following exposure to ultraviolet irradiation by the sun—known as irradiated 7-dehydrocholesterol or vitamin D_3. The formula for vitamin D_3 is shown in Fig. 3. Vitamin D is a white crystalline material, soluble in organic solvents (fat soluble) and relatively stable to heat, acids, alkali and oxidation. It has not been synthesized but is made commercially by irradiation of the pro-vitamins ergosterol and 7-dehydrocholesterol which are extracted from natural products.

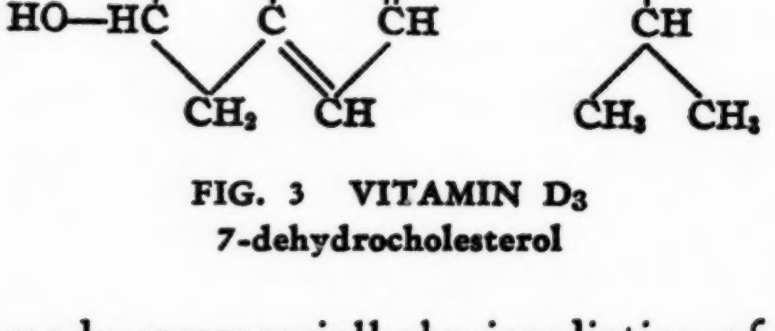

FIG. 3 VITAMIN D_3
7-dehydrocholesterol

Functions: Vitamin D acts as a regulator of calcium and phosphorus metabolism. A deficiency of this vitamin results in the development of rickets in infants and children and of osteomalacia in adults. Both of these are disturbances of bone formation. Rickets is characterized by failure of the osteid tissue to lay down essential calcium salts in growing bone. As a result, growth is retarded and the ribs become distorted (beaded). The breast bone is abnormally curved. The abnormally soft bones of the legs and arms result in bowing of these appendages. Wrists and elbows are enlarged. There is delayed closing of the fontanelles and retarded tooth eruption, softening of the skull and bulging of the forehead. These skeletal deformities are the result of muscle tensions on the softening bone.

Osteomalacia, the adult form of vitamin D deficiency, is a disease characterized by loss of calcium from the bones and resulting in skeletal deformities similar to those of rickets. The mechanism involved in this loss is not clear. Administration of vitamin D is a specific cure for both rickets and osteomalacia. Decreased blood levels of calcium and especially of phosphorus accompany vitamin D deficiency. Tetany is sometimes a complicating factor

in rickets. It is caused by the decreased calcium level of the blood and responds rapidly to vitamin D therapy. There have been reports on the possible value of massive doses of vitamin D in treating dental caries, arthritis, delayed healing of fractures and skin disease, psoriasis. The value of vitamin D therapy in these cases remains dubious and controversial.

Requirements: The human requirements of vitamin D are difficult to estimate correctly because of individual variations in the utilization of dietary calcium and phosphorus without added vitamin D. The optimum amount for babies, children and adolescents is believed to be about 400 I.U. per day, provided sufficient amounts of calcium and phosphorus are included in the diet. The best combination of the necessary minerals with vitamin D is found in milk, which may be fortified with the vitamin. The need of adults appears to be somewhat less, but 400 I.U. serves as a guiding standard. Pregnant and lactating women are advised to double this amount to 800 I.U. per day. The needs of premature babies and twins are also heightened. The vitamin D requirement of poultry has been studied quite extensively because of its practical importance and is usually expressed in vitamin D per pound of feed. About 180 A.O.A.C. chick units* of vitamin D per pound of total feed is recommended for growing chicks; 360 A.O.A.C. units for laying stock, and 540 A.O.A.C. units for breeding stock. Turkeys require at least twice as much vitamin D as chicks. Pigs, sheep, cattle, horses and dogs also require vitamin D for the prevention of rickets, the amounts required varying with body weight.

Early reports on vitamin toxicity were found to be inaccurate, the toxicity being traced to impurities in the commercial preparations. Improved methods of manufacture have eliminated such hazards from modern products. Extremely massive doses of vitamin D, however, may be toxic. The symptoms of toxicity are deposition of calcium in various organs and tissues such as the kidney, heart, blood vessels and stomach. Early symptoms are loss of appetite, vomiting and diarrhea. A continued daily dose of about 20,000 I.U. per kilogram of body weight may be considered toxic to man (3,500 times the average daily requirement). Up to 1,000,000 I.U. *once* every three to six months have been administered without injury in the so-called "shock therapy" treatment of rickets.

Sources: Fish liver oils, sardines, herring, irradiated and fortified milk, butter and fortified margarines, egg yolk; exposure of skin to sun or ultraviolet light; pharmaceutical preparations such as cod liver oil.

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*The A.O.A.C. unit represents a value obtained by the chick assay method because chicks utilize only vitamin D_3. The rat assay method, expressed in I.U., measures both D_2 and D_3.

Vitamin E:

Vitamin E, often referred to popularly as the "anti-sterility" vitamin, is the term used to refer to a group of substances having similar biological actions. These are alpha, beta and gamma tocopherol and a recently reported delta tocopherol. Of these, alpha tocopherol is the most potent and serves as the standard for expressing vitamin E potency. Alpha tocopherol has been synthesized and possesses the following structural formula:

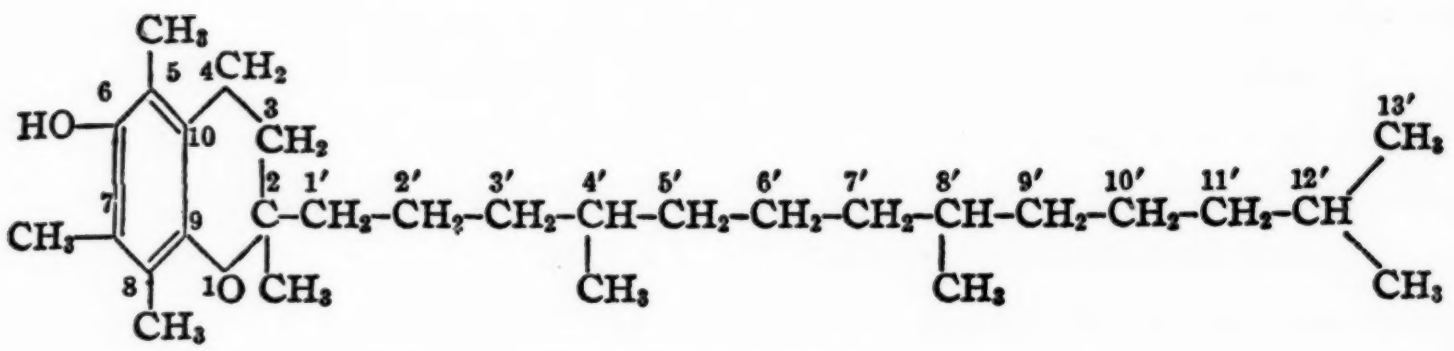


FIG. 4 VITAMIN E — alpha tocopherol

Alpha tocopherol is a slightly yellow oil, a phenol, soluble in fat solvents and fairly stable. It is slowly oxidized by air, but itself possesses anti-oxidant properties which make it useful in preserving other easily oxidizable vitamins in mixtures or in food products.

Functions: The metabolic function of vitamin E is a subject of considerable controversy. One theory, however, although still unconfirmed, seems to offer a logical means of correlating the diverse, apparently unrelated manifestations of vitamin E deficiency. This theory maintains that the primary role of the vitamin is as a regulator of metabolic activities in the cell nucleus, particularly with the processes of cell maturation and differentiation. The significance of vitamin E in human nutrition is not yet conclusively established. In the rat, the most characteristic symptoms of vitamin E deficiency are interruption of pregnancy in the female by resorption of the embryo and neuromuscular disturbances and degeneration of testes in the male. All of these changes occur in tissues which are undergoing rapid growth or high cellular activity. Vitamin E has been reported to be of value in treating the muscular dystrophy in sheep known as "stiff lamb disease." Vitamin E was thought to be of value in treating sterility and early abortion in cattle, and Bang's disease (infectious abortion), but this is still a matter of dispute. Vitamin E is used empirically and purely on an experimental basis in clinical medicine in the treatment of habitual and threatened abortion, premature separation of the placenta, certain toxemias of pregnancy, various muscular dystrophies and neuro-muscular diseases. The results have been

exceedingly variable, so that no definite conclusion can be reached as yet with regard to the efficiency of or necessity for the vitamin in the human economy.

Requirements: Vitamin E is necessary for mice, rats, guinea pigs, rabbits, dogs, chicks and ducks. In rats, the male animal requires about one-seventh to one-tenth the amount needed by the female. The average daily requirement of the female rat is from 2-3 mg. of alpha tocopherol; the minimum fertility requirements of the female are 15 mg. per kilogram of body weight per day. About 6 mg. per day has been recommended for clinical dosage in human cases of spontaneous abortion. The tocopherols are non-toxic substances even in high dosages.

Sources: Wheat germ oil, cottonseed oil and other vegetable oils, except olive oil; lettuce, green leafy vegetables, whole grains. Small amounts are present in oranges, bananas, meat, milk and eggs. Vitamin E is available commercially in the form of concentrates from natural sources and in the form of the racemic mixture, *dl*-alpha tocopherol obtained by synthesis. This latter form, often sold as the more stable acetate, is preferred for clinical use. It is more than twice as potent as natural alpha tocopherol.

Antagonists: The compound, alpha tocopherol quinone which is related structurally to both vitamin E (alpha tocopherol) and vitamin K (2-methyl-1,4-napthoquinone) interferes with the action of vitamin E in female rats by competitive inhibition. Strangely enough, however, vitamin E deficiency (termination of pregnancy by resorption of the embryo) induced by the feeding of alpha tocopherol quinone responds only to treatment with vitamin K and not to vitamin E.

Ascorbic Acid:

Ascorbic acid is known also as vitamin C, the anti-scorbutic or anti-scurvy vitamin, or cevitamic acid. It is the lactone form of hexuronic acid and is represented by the structural formula shown in Fig. 5. Ascorbic acid is an optically active compound occurring, therefore, in the *l*- and *d*- forms of which only the *l*- form is biologically active. It is water soluble and, in solution, is rapidly oxidized upon contact with air. It is protected from oxidation in acid media and destroyed in alkaline media. For this reason acid foods (oranges, tomatoes) retain their vitamin C potency much better than

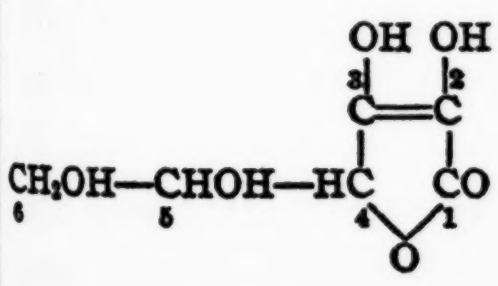


FIG. 5 *l*-ASCORBIC ACID

other foods such as green vegetables. Vitamin C is the least stable of the vitamins and is rapidly destroyed by improper storage of foods and cooking processes. If vegetables are cooked in the absence of air (covered tightly or in pressure cooker) and in acid medium, most of the vitamin is preserved; cooking in uncovered vessels or in alkaline media causes rapid loss of vitamin C.

Storage of foods at room temperature results in marked loss of the vitamin. Under adequate conditions of refrigeration the vitamin is well retained, although converted to dehydroascorbic acid. Because early methods for detecting vitamin C failed to record the presence of the dehydro form, it was thought that vitamin C was lost during storage under refrigeration. It is now recognized, however, that dehydroascorbic acid is nutritionally available.

Functions: There is considerable evidence that ascorbic acid acts as an enzyme or enzyme constituent in the metabolism of aromatic amino acids (tyrosine, phenylalanine). This enzyme action is thought to be of an oxidation-reduction nature because ascorbic acid is easily reversibly oxidized to dehydroascorbic acid. Vitamin C seems to be essential for proper formation and maintenance of intercellular material such as the collagen of all fibrous tissues, the cement substance of endothelial tissues (particularly of blood capillaries), and the matrix of bone, dentin and cartilage. The resorption of these intercellular materials in the absence of vitamin C explains the nature and widespread distribution of the lesions of scurvy.

Vitamin C deficiency, if severe, results in scurvy. The disease is characterized by weakness, spongy gums, loose teeth, resorbed dentin, swollen, tender joints and hemorrhages in various tissues. In the United States, infantile scurvy is the most prevalent form of the disease. It is particularly characterized by disturbances in bone formation. The scorbutic infant exhibits swelling and tenderness of the thighs, a disinclination to move, irritability, fretfulness, pallor and a worried expression. Milder deficiencies may result in gingivitis, pallor, weakness, vague pains in the extremities, loss of weight. Delayed healing of wounds, ulcers and fractures is thought to be another complication of vitamin C deficiency. It may be of value in diseases such as tuberculosis and rheumatic fever where it may enhance the healing process. Reports, not wholly confirmed, have been made concerning the effectiveness of vitamin C in bronchial asthma and hay fever and as a detoxicant in heavy metal poisoning.

Requirements: The vitamin C requirements of various species differ with their ability to synthesize the vitamin internally. Rats, chicks and ruminants, for example, have no need for dietary ascorbic acid, whereas guinea pigs and man require daily provision of the vitamin in food. Recommended daily allowances for adults range from 30 mg. (minimum) to 75 mg. (optimum). An intake of 30 mg. per day is recommended for infants; 35-75 mg. for children and 80-100 mg. for adolescents. The daily requirements are increased to 100 mg. during pregnancy and 150 mg. during lactation. There is no evidence of toxicity resulting even from very large doses of ascorbic acid.

Sources: Citrus fruits (orange, grapefruit, lemon); tomatoes, pineapple, raw or *properly cooked* green vegetables; potatoes; raw liver; currants, honeydew melon, strawberries. Unusually potent natural sources of vitamin C have been reported and utilized during the war. These include guava (jelly, paste, powder), rose hips, unripe green walnuts, pine needle extracts.

Antagonists: The action of vitamin C can be inhibited by glucoascorbic acid, a synthetic compound closely related in structure to the vitamin. It is interesting to note that rats, normally immune to scurvy, have been made scorbutic by feeding of glucoascorbic acid.

Vitamin K:

The term vitamin K refers to a group of substances of the naphthoquinone class which have similar biological activity. The vitamin is known also as the antihemorrhagic vitamin or "Koagulationsvitamin" (Danish), from which latter term the symbol K was derived. Natural vitamin K_1 has been isolated from alfalfa and has also been synthesized. It is 2-methyl-3-phytyl-1,4-napthoquinone. Vitamin K_2 is obtained from putrefied fish meal and is 2-methyl-3-difarnesyl-1,4-naphthoquinone. Even more potent than the naturally occurring compounds is the naphthoquinone derivative 2-methyl-1,4 naphthoquinone which has been named "menadione" and serves as the standard for expressing potency of vitamin K. The formula for synthetic vitamin K_1, menadione, is shown in Fig. 6. Vitamin K is fat-soluble, stable to heat, destroyed by oxidation, acids, alkalis and exposure to light. It cannot be absorbed and utilized in diseases where there is a deficiency of bile secretion such as obstructive jaundice. When given orally, vitamin K must be administered in conjunction with bile salts. Newly developed water-soluble forms of vitamin K can be administered successfully without bile salts.

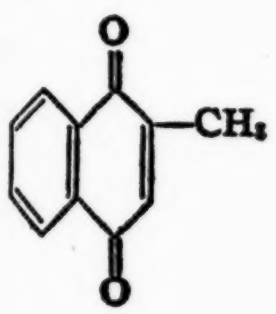


FIG. 6 VITAMIN K (Menadione). 2-methyl-1, 4-naphthoquinone.

Functions: Vitamin K is essential for the formation in the body of prothrombin, a constituent of the blood which plays a major role in the process of blood coagulation. A deficiency of vitamin K leads to a lowering of the level of prothrombin in the blood (hypoprothrombinemia) with a resultant prolongation of the normal clotting time of the blood. The condition is manifested clinically by persistent hemorrhages. It is found in hemorrhagic disease of the newborn, in diseases of the biliary tract especially following operations, in various intestinal disorders, in non-tropical sprue and in certain cases of nutritional deficiency. Hemophilia, the "disease of royalty," is not related to vitamin K or prothrombin deficiency and cannot be treated with vitamin K.

Hemorrhagic disease of the newborn, a frequently fatal disease manifested by cerebral hemorrhages, can be prevented by administering vitamin K to the mother shortly before the child is born or to the newborn infant itself. During the first week of life until the intestinal flora are established by the ingestion of food all newborn infants have a "physiological" hypoprothrombinemia due to the absence of vitamin K, and are therefore in potential danger of succumbing to hemorrhages. Vitamin K prophylaxis for the new born is now routine in almost all obstetric practice. Vitamin K and bile salts are routine therapy in the pre- and post-operative care of patients with obstructive jaundice or other lesions of the biliary tract which interfere with proper utilization of vitamin K, thereby eliminating the greatest single cause of post-operative death (uncontrollable hemorrhage) in these cases. Vitamin K has been reported to be of value in miscellaneous other hemorrhagic disorders, but these claims have not been substantiated. A recent development has demonstrated the efficiency of vitamin K in inhibiting the formation of acid from sugar in the saliva. Since it has been observed that rapid acid formation in the mouth may be a factor in producing dental caries, it has been suggested that the incorporation of vitamin K in candy or gum might have a preventive effect on the development of caries.

Requirements: Vitamin K is required by all animals and by a few microorganisms. It is not necessary for yeasts, fungi and most bacteria. The daily requirements are not known. Vitamin K is probably supplied in adequate amounts by intestinal synthesis. The therapeutic dose for the prevention or cure of hypoprothrombinemia is 1-2 mg. of menadione per day, orally or intramuscularly. (Water-soluble vitamin K may be administered intravenously.) Oral menadione requires the accompanying administration of 20-30 grains of ox bile salts for proper assimilation of the vitamin. Naturally occurring K_1 and K_2 are non-toxic even in large doses. Synthetic menadione

and other forms may be toxic to man and animals in excessive amounts. Symptoms of toxicity are vomiting and excretion of porphyrins, occasionally albumin, in the urine. It is recommended that the daily dose of menadione should not exceed 2 mg. and that administration should not be continued for more than 28 days.

Sources: Natural vitamin K is derived from alfalfa, kale, spinach, dried carrot tops, tomatoes, chestnuts, soybean oil, putrefied fish meal, bran and casein. It is also available in synthetic form as menadione.

Antagonists: Vitamin K deficiency is incurred in cattle by the ingestion of spoiled sweet clover hay which contains dicoumarol. The powerful fungicide, 2,4-dichloro-naphthoquinone, developed during the war, is a structural antagonist of the vitamin and conversely, the presence of vitamin K reverses the fungicidal action of this compound. Vitamin K deficiency can be induced experimentally by feeding sulfonamides, and may be an untoward clinical complication of sulfonamide therapy in man. The mechanism involved is apparently an interference with the activity of intestinal microorganisms which synthesize vitamin K. The salicylates also act as antagonists of vitamin K. For this reason, prolonged dosage with aspirin may require co-administration of vitamin K to prevent possible hemorrhagic reactions. It is believed that the antagonist action of dicoumarol may be due to its degradation to salicylic acid in the body.

Vitamin P and Rutin:

Vitamin P, originally discovered in extracts of paprika, is known also as the "permeability" vitamin. Vitamin P is a crude extract which contains, besides other physiologically active compounds, the flavone glucosides eriodictin and hesperidin. The active fraction of vitamin P as extracted from lemon peels is a mixture of these two glucosides known as citrin. Grapes are said to be the richest natural source of vitamin P. Rutin is another flavone-derivative glucoside which occurs principally in tobacco leaves and buckwheat. It is reported to have physiological activity similar to that of vitamin P and resembles hesperidin closely in chemical structure:

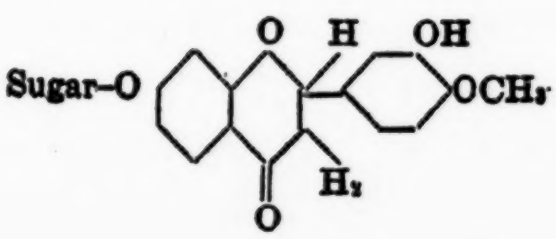
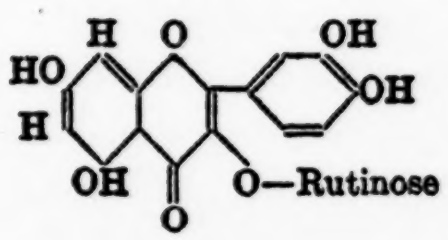


FIG. 7 HESPERIDIN
(Component of vitamin P)



RUTIN

Functions: Both vitamin P and rutin are believed to play a role, distinct from that of vitamin C, in protecting against capillary fragility and permeability. It has also been suggested that rutin may be important in preventing certain of the vascular accidents which sometimes occur in cases of high blood pressure and might conceivably be caused by an abnormal condition of the capillaries. The vitamin nature and behavior of both vitamin P and rutin are still to be conclusively established.

Miscellaneous Vitamins:*

Vitamin B_3: A pigeon growth factor occurring in liver, yeast, whole grains and malt. It is a water-soluble filtrate factor probably identical with pantothenic acid.

Vitamin B_4: An anti-paralysis factor for rats and chicks, occurring in yeast, liver, dried grass, wheat germ, pork brain and kidney. It may be identical with a mixture of arginine, cystine and glycine, since a deficiency of these amino acids causes closely similar symptoms in the chick.

Vitamin B_5: A weight maintenance factor for pigeons, probably associated with pyridoxine and identical with nicotinic acid. Occurs in yeast eluates.

Vitamin B_7 (Factor I): An alcohol soluble factor preventing digestive disturbances in pigeons. Occurs in rice polishings and may be identical with pyridoxine.

Vitamin B_8: Adenylic acid (or its derivative adenine), a factor in muscle tissue and yeast thought to be necessary for certain strains of lactic acid bacteria and to increase the efficacy of nicotinic acid in pellagrins. Believed to be an essential component of several enzyme systems.

Vitamin B_{10} and B_{11}: Unidentified factors required for proper feathering and growth of chicks. One of these may be related to or identical with folic acid.

Vitamin Bp: A factor essential for the prevention of perosis or "slipped tendon" in chicks. Apparently distinct from either manganese or choline, both of which are effective anti-perosis agents.

Vitamin J: A postulated anti-pneumonia factor in lemon juice, black currants, rowanberries and elderberries, apparently distinct from either vitamin C or vitamin P. Sometimes called vitamin C_2. Guinea pigs infected with pneumococci show remarkable resistance to the disease when lemon juice is administered.

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*The essential fatty acids, sometimes inaccurately described as "vitamin F," will be discussed in a future issue on fat metabolism.

Vitamin L: Two factors L_1 and L_2, occurring in liver and yeast, respectively, and apparently essential for the initiation of normal lactation in the rat. The factors are not mutually replaceable. Much higher amounts of these factors are necessary to induce the first lactation than are necessary for a second litter. The vitamins seem to be important in the maturation of lactation tissue.

Factor T: A fat-soluble factor, sensitive to ultraviolet irradiation, whose absence causes a decrease in blood platelets (thrombocytosis) in rats and man. It occurs in sesame oil and egg yolks.

Grass Juice Factor: A water-soluble factor essential for growth and reproduction of rats, rabbits and guinea pigs. Occurs chiefly in fresh young grass and its juice. Cereal grasses, rye grass, young white clover, peas, pea shells, cabbage, turnip tops, spinach and summer milk are good sources. It is destroyed by heat and oxidation; preserved in forage by acid methods of ensiling.

Anti-Gizzard Erosion Factor: A fat-soluble, heat-labile factor in kale, wheat bran and middlings, liver, kidney and lung tissue. It prevents erosions in the lining of chick gizzards presumably caused by a lack of bile which contains cholic acid. It may be chondroitin sulfuric acid.

Guinea-Pig Anti-Stiffness Factor: A fat-soluble factor occurring in raw cream and raw whole milk, but not in pasteurized milk, and in sugar cane juice. Believed to prevent and cure a deficiency syndrome in guinea pigs characterized by a stiffness of the wrists and ending ultimately in emaciation and death. One gram of raw cream per day was found to cure the disorder in five days. Active concentrates have been obtained from raw cream and a crystalline material from sugar cane juice, but it is not certain whether the two materials are chemically identical. The factor is apparently involved in phosphate metabolism. The existence of this factor has not been confirmed by other investigators and no reports concerning its import in human nutrition have appeared.

Guinea Pig Factors 1, 2 and 3: Unknown factors "G.P.F.-1," "G.P.F.-2" and "G.P.F.-3" are required by guinea pigs. "G.P.F.-1" has been identified as folic acid. "G.P.F.-2" is not a single factor, but is replaceable by a mixture of cellulose, arginine, cystine and glycine. "G.P.F.-3" has been concentrated but not identified.

Strepogenin: An unidentified microbial growth factor present in enzymatic protein digests or hydrolysates, probably a polypeptide in structure. It appears to be closely related to, but not identical with, glutamine and asparagine.

Recommended Dietary Allowances

Food and Nutrition Board, National Research Council

	Calories	Protein grams	Calcium grams	Iron mg.	Vitamin A I.U.	Thiamin (B_1) mg.	Riboflavin mg.	Niacin (Nicotinic acid) mg.	Ascorbic acid mg.	Vitamin D I.U.
Man (70 Kg.)										
Sedentary	2500	.....	.....	.....	.....	1.5	2.2	15	.....	.....
Moderately active	3000	70	0.8	12	5000	1.8	2.7	18	75	
Very active	4500	.....	.....	.....	.....	2.3	3.3	23	.....	.....
Woman (56 Kg.)										
Sedentary	2100	.....	.....	.....	.....	1.2	1.8	12	.....	.....
Moderately active	2500	60	0.8	12	5000	1.5	2.2	15	70	
Very active	3000	.....	.....	.....	.....	1.8	2.7	18	.....	.....
Pregnancy (latter half)	2500	85	1.5	15	6000	1.8	2.5	18	100	400 to 800
Lactation	3000	100	2.0	15	8000	2.3	3.0	23	150	400 to 800
Children up to 12 years:										
Under 1 year	100/Kg.	3 to 4/Kg.	1.0	6	1500	0.4	0.6	4	30	400 to 800
1–3 years	1200	40	1.0	7	2000	0.6	0.9	6	35	
4–6 years	1600	50	1.0	8	2500	0.8	1.2	8	50	.....
7–9 years	2000	60	1.0	10	3500	1.0	1.5	10	60	.....
10–12 years	2500	70	1.2	12	4500	1.2	1.8	12	75	.....
Children over 12 years:										
Girls, 13–15 years	2800	80	1.3	15	5000	1.4	2.0	14	80	
16–20 years	2400	75	1.0	15	5000	1.2	1.8	12	80	.....
Boys, 13–15 years	3200	85	1.4	15	5000	1.6	2.4	16	90	
16–20 years	3800	100	1.4	15	6000	2.0	3.0	20	100	.....